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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/013,895	01/27/98	NI J	PF355

022195
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HM12/0508

EXAMINER	
KAUFMAN, C	
ART UNIT	PAPER NUMBER
1646	28

DATE MAILED: 05/08/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/013,895	Applicant(s) NI ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/16/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *178-191, 194 and 198-208* is/are allowed.

6)☒ Claim(s) *22, 23, 26, 32, 37-43, 48, 49, 55-70, 72, 75-81, 84-88, 92-105, 108-114, 118, 120, 121, 123, 128-141, see Continuation Sheet* is/are rejected.

7)☐ Claim(s) *24, 25, 27-31, 33, 35, 36, 44-47, 50, 51, 53, 89, 122, 124, 126, 127, 160, 161 and 165-168* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 22-33,35-51,53,55-70,72,75-81,84-89,91-105,108,114,118,120-124,126,141,144-152,156,158-161,165-173,176-195 and 198-219.

Contiunation of rejected claims: 144-152, 156, 158, 159, 169-173, 176, 177, 192, 193, 195, 209-219

DETAILED ACTION

The amendment filed 2/16/01 has been entered.

Response to Arguments

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims or in view of Applicant's arguments.

The rejection of claim 195 under 35 USC 112, first paragraph is withdrawn in view of the amendment to the claim.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 194 is objected to because of the following informalities: in the last line, "a" after "wherein" should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim176 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 176 as it now stands recites in line 3, "contacting a polypeptide with ....". It is unclear which polypeptide is being contacted, that is, the expressed polypeptide or another host cell polypeptide. It appears that in amending the claim, a typographical error was introduced, resulting in a change "said" to "a" after "contacting".

Claim Rejections - 35 USC § 112

Claims 22, 23, 26, 32, 37-43, 48, 49, 55-70, 72, 75-81, 84-88, 92-105, 108-114, 118, 120, 121, 123, 128-141, 144-152, 156, 158, 159, 169-173, 177, 193, 195, 209-219 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide i) that encodes the polypeptide of SEQ ID NO:2 or ii) is at least 90% identical to a polynucleotide that encodes the polypeptide of SEQ ID NO:2 and binds TRAIL or induces

apoptosis or iii) is at least 90% identical to a polynucleotide that encodes the extracellular domain (ECD) of the polypeptide of SEQ ID NO:2 and binds TRAIL or iv) is at least 90% identical to the polynucleotide of SEQ ID NO:1 or a specified fragment thereof and hybridizes under the conditions specified in claim 195 to SEQ ID NO:1 and is usable as a probe for specifically detecting the nucleic acid of SEQ ID NO:1 or v) encodes a fragment of SEQ ID NO:2 that binds an antibody with specificity for the polypeptide consisting of amino acids 24-468 of SEQ ID NO:2, does not reasonably provide enablement for a polynucleotide that is not identical to SEQ ID NO:1 but must still encode a polypeptide or that is less than 100% identical to a polynucleotide encoding the polypeptide of SEQ ID NO:2 or that is less than 100% identical to the polynucleotide of SEQ ID NO:1 or the portion thereof encoding the ECD without the requirement that it hybridize under specified conditions so it must have the function of a probe or that is identical to a fragment of SEQ ID NO:1 (*e.g.*, 50 contiguous nucleotides) but has no **recited** function (*e.g.*, encoding a known epitope or as a probe). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to:1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims rejected above are drawn to i) either a polynucleotide not identical to SEQ ID NO:1 or a polynucleotide encoding SEQ ID NO:2, wherein the claimed polynucleotide has no function or a function not commensurate in scope with the limited structure required by the claims, ii) or a polynucleotide identical to only a fragment of SEQ ID NO:1 or the encoding polynucleotide, wherein the claimed polynucleotide has no stated function.

While a polynucleotide need not encode a polypeptide, it must at least be usable by one skilled in the art as a probe to detect specifically the disclosed naturally occurring DR4-encoding sequence of SEQ ID NO:1. One skilled in the art would not choose a nucleic acid as a probe that is not capable of such specific detection and the skilled artisan would not know how to use a

probe without specificity. If the polynucleotide does encode a protein, the skilled artisan must be able to use the encoded polypeptide without undue experimentation. The specification does not provide guidance about which amino acids within particular domains are necessary for the claimed functions. The specification provides very limited guidance, though no examples, for using polypeptides not identical to SEQ ID NO:2 or comprising only a fragment of SEQ ID NO:2. For example, the skilled artisan could us a fragment of SEQ ID NO:2 if it was bound by an antibody that specifically binds amino acids 24-468 of SEQ ID NO:2, because that fragment would necessary comprise an antibody specific epitope. The skilled artisan could also use a polypeptide sharing reasonably high identity with SEQ ID NO:2 or the ECD or ICD (intracellular domain) thereof if that polypeptide had a specified function such as binding TRAIL or being able to substitute for the corresponding portion in SEQ ID NO: 2 induce apoptosis or bind TRAIL (*e.g.*, claim 89).

Claims drawn to polynucleotides at least 90% identical to a nucleic acid encoding a polypeptide with a specific amino acid sequence do not need to closely resemble the disclosed encoding polynucleotide because of codon degeneracy. Therefore, polynucleotides that are neither useful as specific nucleic acid probes nor as encoding functional polypeptides are encompassed by the instant claims, but they are not enabled by the specification or prior art for how to use them. These types of claims would be enabled if the structural relatedness of the claimed polynucleotide was sufficiently close to that of SEQ ID NO:1 so that the skilled artisan could use it as a probe for specific detection of SEQ ID NO:1 without undue experimentation and the claims made that function clear.

Other claims are drawn to a polynucleotide that has some resemblance to the disclosed encoding polynucleotide, for example being 90% identical to SEQ ID NO:1, but also has to encode a polypeptide (or fragment). If the claimed polynucleotide does not have to encode a *functional* polypeptide (*e.g.* claim 158), then one skilled in the art does not know how to use either the polynucleotide or the encoded polypeptide which has no specific function. The specification does not teach how to use such polynucleotides even though they are encompassed by the present claims. The structural diversity of the claimed polynucleotides gives great breadth. These types of claims would be enabled if the claimed polynucleotide encoded a polypeptide with sufficient structural relatedness to SEQ ID NO:2 and a function specific to the polypeptide

of SEQ ID NO:2 (*e.g.*, specifically binding TRAIL) so that the skilled artisan could use the encoded polypeptide without undue experimentation.

Still other claims are drawn to polynucleotides encoding a fragment of SEQ ID NO:2 that is not the full ICD (a.k.a. death domain) but that induces apoptosis. The portion of DR4 encoding the ICD from amino acid 265-468 of SEQ ID NO:2 (p. 5, lines 27-28). There are no examples in the specification (Example 5) or prior art of DR-type polypeptides inducing apoptosis with less than the full ICD. The prior art (Chinnaiyan et al., Science, 1996, of record) discloses DR3, showing only that the whole receptor bound another protein (TRADD, p. 991, third paragraph). For the DR3 receptor, it was shown that without the death domain, DR3 could not induce apoptosis (Chinnaiyan et al., p. 992, first paragraph). Because so little was known about how TRAIL-like receptors function in terms of ligand binding--both about which ligand(s) they bind and what portion(s) of the ECD is necessary for that binding, and how apoptosis is induced in terms of signal transduction and what portion(s) of both the death domain and the receptor as a whole is necessary for induction of apoptosis, the relative skill of those in the art pertinent to the instant invention is not high.

In view of the reasons above, which include: of the limited guidance in the specification, the lack of examples in the prior art and specification, the breadth of the claimed polynucleotides extending beyond the complete ECD or full length natural receptor encoding sequence and the relative skill of those in the art, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Claims 192 and 176 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using a host cell that expresses a polynucleotide encoding at least the ECD of SEQ ID NO:2 or that expresses a polypeptide at least 90% identical to the ECD of SEQ ID NO:2 and binds TRAIL, does not reasonably provide enablement for methods using host cells expressing polynucleotides encoding polypeptides without the above identity and function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In order to practice the claimed method, the expressed polynucleotide must encode a

polypeptide that binds TRAIL. There is no other known or disclosed ligand for the DR receptor. There is no guidance for using a polypeptide in the claimed method that does not bind TRAIL. There is no guidance as to what amino acids within the ECD are necessary for binding. Ligand binding is a complex event requiring the receptor to not only have particular amino acids that directly contact the ligand, but also amino acids that are responsible for providing the proper conformation of the contacting amino acids. It is unpredictable what ligand besides TRAIL the expressed polypeptide would bind. If the polypeptide cannot bind TRAIL, it would require undue experimentation to practice the claimed method.

Applicants' arguments pertinent to the new rejections above are addressed here. Applicants argue that the specification teaches that a great deal is know about the ligand-binding domain of TNF receptors, such as conserved cysteine residues, and effects of deletion up to amino acid 132 or after 221, so one could predict which amino acids between 131-222 of SEQ ID NO:2 are required for binding. The argument has been fully considered, but is not persuasive. The conservation of a cysteine does not provide information on which amino acids besides that cysteine are necessary for ligand binding. That leaves 213 amino acids in this receptor that may or may not be necessary. Because the TNF family of receptors bind a wide non-coextensive variety of ligands with distinct binding properties. One cannot predict with assurance which amino acids are required for binding for the DR subfamily of receptors since so little is known about the structural specifics of its ligand binding. There has been no showing for DR receptors that deletion of any number of amino acids from the N-terminal or C-terminal can be made while retaining TRAIL-binding ability. While deletion may enable retention of "some biological activity such [as] receptor binding", what activity would be retained is unpredictable. As discussed above and in previous Office actions, ligand binding is a complex event involving many amino acid residues in both ligand contact and binding site conformation. For these reasons, one skilled in the art could not predict which amino acids are required for binding.

Applicants argue that TRAIL was in the prior art and available for ligand binding assays so screening and mutagenesis/amino acid substitutions could be used without undue experimentation to make and use the claimed invention. The argument has been fully considered, but is not persuasive. This is an invitation to experiment without a reasonable expectation of

success. One could not know predict what effect an amino acid change would have on binding. As discussed in the rejection above, undue experimentation would be required to practice the claimed invention.

Conclusion

Claims 24, 25, 27-31, 33, 35, 36, 44-47, 50, 51, 53, 89, 122, 124, 126, 127, 160, 161 and 165-168 are objected to as depending on rejected claims.

Claims 178-191, 194 and 198-208 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
May 3, 2001